

Comparative Testing of New Hemostatic Agents in a Swine Model of Extremity Arterial and Venous Hemorrhage

Capt Jared G. Clay, USAF MC*; J. Kevin Grayson, DVM, PhD†; Maj Dustin Zierold, USAF MC*

ABSTRACT Objective: To compare advanced hemostatic dressings: HemCon (HC), QuikClot ACS+ (advanced clotting sponge, and two granular agents: Celox (CX) and WoundStat (WS), with a standard field dressing in a swine model of extremity hemorrhage. Methods: We randomized 30 animals to treatment with a standard dressing or a hemostatic agent applied to a 2 × 6-mm injury in the femoral artery and vein after 45 s of free bleeding. Animals received 500 mL Hextend 15 min after the bleeding commenced without further resuscitation. End point was survival to 120 min or non-survivable blood pressure. Results: Survival to 120 min among treatment groups was 100% (WS), 83% (CX), 67% (HC), and 50% (ACS+). No control animals survived. Postinjury blood loss (mL/kg) was 4.6 (WS), 12.9 (CX), 10.0 (HC), and 15.8 (ACS+) compared to 27.0 for controls. Conclusion: All hemostatic dressings result in significantly less blood loss and improved survival over standard gauze dressing.

INTRODUCTION

Uncontrolled bleeding is the leading cause of death in military trauma cases^{1,2} and the second leading cause of death in civilian trauma.³ In recent military operations, hemorrhage resistant to standard hemostatic techniques continues to be the number one cause of battlefield death.⁴ Early and effective control of hemorrhage can theoretically save more lives than any other measure.⁵ The mortality from traumatic injuries has diminished markedly in recent military operations, due to several factors including routine wear of body armor, judicious use of tourniquets for extremity hemorrhage, rapid casualty evacuation, and aggressive use of blood products in hemorrhagic shock.⁶ Advanced hemostatic agents further reduce hemorrhage and death when applied to wounds not amenable to treatment with a tourniquet.

The ideal hemostatic agent, as defined by Pusateri and colleagues,⁴ should include the ability to rapidly stop large-vessel arterial and venous bleeding even when applied through a pool of blood, be ready for use with no mixing or special preparation, simple to apply, lightweight, and durable, stable at various temperatures and humidities, harmless to both the wounded individual and the one giving aid, and inexpensive.

Several advanced hemostatic agents have been developed with varying mechanisms of action. Many of these have proven effective in a variety of injury models.⁷⁻²² We conducted a randomized study comparing four hemostatic agents that are FDA approved for the treatment of external hemorrhage and have proven efficacy (Table I). We used a bulky gauze con-

trol dressing for reference in a swine model of lethal groin injury—a similar model that has been used in previous tests of hemostatic agents.¹⁵⁻²³ Our goal was to compare the efficacy of these agents with regard to blood loss, maintenance of blood pressure, survival, and wound site temperature in a model that avoided intensive fluid therapy, thereby approximating prehospital conditions.

MATERIALS AND METHODS

This study was approved by the Institutional Animal Care and Use Committee and all animals received humane care in compliance with the *Guide for the Care and Use of Laboratory Animals* (National Institutes of Health publication 86-23, revised 1996). All animal handling and research was conducted in our facility, which is accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care International. The office of the Surgeon General of the Air Force provided all funding for this study.

Hemostatic Agents

We compared several hemostatic agents with demonstrated efficacy that had been FDA approved for control of external hemorrhage. We used a standard army field dressing (AFD) (Conterra Inc., Bellingham, Washington) as a control dressing. This is a bulky gauze dressing with bandage straps, which were removed before use in this study. An AFD was also applied over each of the hemostatic agents to enhance blood collection and distribute pressure.

Enhanced HemCon (HC) dressing (HemCon Medical Technologies, Inc., Portland Oregon) is a 4 × 4-inch lightweight chitosan dressing that is nontoxic. Its primary mechanism of hemostasis is a strong adherence to tissue when wet with blood or other fluid, thus creating a seal and preventing further hemorrhage. Several studies have reported its efficacy.^{9,13,24} HemCon has modified the dressing to be thinner and more pliable to create a better seal. The dressing was FDA approved in February 2003 and is currently deployed by the U.S. Army.

*David Grant Medical Center 60MSG/SGCQ 101 Bodin Circle, Travis AFB, CA 94535.

†David Grant Medical Center, Clinical Investigation Facility, 60MDSS/SGSE 101 Bodin Circle, Travis AFB, CA 94535.

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TABLE I. Hemostatic Agents

Agent	Form	Mechanism of Action
Army Field Dressing	Gauze	Absorption
QuikClot ACS+	Zeolite granules contained in a porous bag	Zeolite granules rapidly absorb water upon contact with blood, concentrating platelets and clotting factors.
Enhanced HemCon	Single-sided chitosan wafer	Positively charged chitosan forms strong seal with negatively charged blood cells upon contact.
Celox	Fine chitosan granules	Positively charged chitosan granules bond with negatively charged blood cells forming a gel-like seal in the wound.
WoundStat	Smectite granules	Smectite granules rapidly absorb water upon contact with blood, concentrating platelets and clotting factors; granules form a clay-like seal in the wound.

QuikClot ACS+ (advanced clotting sponge) (Z-Medica, Wallingford, Connecticut) is a modified version of the original zeolite granules that act by rapid absorption of water—concentrating platelets, red blood cells, and clotting factors in an exothermic reaction. ACS+ is packaged in a porous fabric bag of four compartments to ease product removal. The zeolite granules have been modified to diminish the amount of heat generated. A recent study demonstrated that ACS was as effective as the original QuikClot beads in providing hemostasis and improving survival.²⁰ ACS+ was FDA approved in July 2006. QuikClot products are currently deployed by multiple branches of the U.S. Armed Forces as part of a standard first aid kit.

Celox (CX) granules (Medtrade Products Ltd., Crewe, United Kingdom) are chitosan-based granules that were FDA approved in June 2006. They are positively charged particles that attract to negatively charged red blood cells and subsequently undergo chemical and mechanical linkages to form a barrier at the site of injury. The efficacy of these granules have recently been reported in a large animal model.²²

WoundStat (WS) granules (TraumaCure, Bethesda, Maryland) is a smectite-based granular product approved by the FDA in August 2007. It acts partially by rapid absorption of water that causes the granules to swell and take on a clay-like consistency with tissue adherence properties. The granules are negatively charged, which may also activate the intrinsic clotting pathway. This dressing has proven efficacy in recent tests.^{19,23}

Animal Handling and Preparation

We used 30 female or castrate male Yorkshire crossbred commercial swine (*Sus scrofa*), weighing 43 ± 6 kg. The animals were fed a commercial diet and observed for 7 days before initiating the study. The animals were fasted 12 hours before surgery with unrestricted access to water. On the day of surgery, animals were premedicated with tiletamine/zolazepam 4.4 mg/kg IM (Telazol, Fort Dodge Laboratories, Fort Dodge, Iowa) and glycopyrrolate 0.1 mg/kg IM (Baxter Healthcare Corporation, Deerfield, Illinois). Anesthesia was induced with 5% isoflurane in oxygen by nose cone. Endotracheal intubation was followed by 3% isoflurane in oxygen for anesthetic maintenance. Mechanical ventilation was set for tidal vol-

umes of 7–10 mL/kg and a respiratory rate of 10–15 breaths per minute. A rectal temperature probe measured core temperature, which was maintained between 36°C and 38°C with a water-filled warming blanket.

Surgical Procedure

A peripheral arterial catheter was surgically placed in the right saphenous artery and mean arterial pressure (MAP) was transduced continuously. A right neck dissection was performed with insertion of a second arterial catheter into the carotid artery and a 14-gauge catheter into the jugular vein. When suffering hemorrhagic stress, a swine's spleen may actively contract creating an auto-transfusion. To decrease variability from this unpredictable phenomenon (as has been done in similar studies^{18,19,23}), splenectomy was performed via a midline laparotomy, and a volume of lactated Ringer's solution equal to three times the spleen weight was infused. The abdomen was closed with perforating towel clamps. A right groin dissection was then conducted with removal of the adductor muscle overlying the femoral canal, and the femoral artery and vein were isolated. The first four animals in each group had a temperature probe sutured to the muscle and nerve adjacent to the artery. To simulate a near-transection, we used a 2 × 6-mm aortic punch (Scanlan, Saint Paul, Minnesota) to create a standardized injury in both the femoral artery and vein. We allowed 45 s of free bleeding before application of the study dressing. The dressings were studied in random order, and the surgeon was blinded to the dressing until after the wound had been created and free bleeding had occurred.

Animals in the control group had the AFD applied directly to the wound and manual pressure sufficient to stop the bleeding was held for 6 min. The hemostatic agents were applied according to the manufacturers' directions and then covered with an AFD through which manual pressure was applied. Specifically, HC was cut in half to create a 2 × 4-inch dressing and pressure was held for 2 min. ACS+ (100 g) was applied directly to the wound and pressure was provided for 3 min. CX (70 g) was applied and manually formed to the wound followed by pressure for the remainder of 5 min. WS (150 g) was applied and manually formed to the wound followed by pressure for the remainder of 3 min. For granular applications,

molding of the agent generally took 15–30 s. We allowed only a single application of each dressing.

Pressure was then released for all dressings and the AFD and test agent were left undisturbed. Any blood loss was collected into a suction canister. Fifteen minutes after the bleeding commenced, each animal received 500 mL of 6% hetastarch solution (Hextend, Hospira, Inc., Lake Forest, Illinois). No other fluids were given. The animal was monitored under general anesthesia for 2 h or until a nonsurvivable blood pressure was reached, which we defined as a MAP <20 mmHg for 5 min or a MAP <10 mmHg at any time. Upon reaching either end point, a lethal dose of pentobarbital veterinary euthanasia solution (170 mg/kg) was administered intravenously and nonrecovery was ensured with bilateral thoracotomy.

Data Collection

Before injury, we recorded weight, temperature, carotid and saphenous MAP, heart rate, oxygen saturation, complete blood count, fibrinogen, activated clotting time, and arterial blood gases. Dressings and suction canisters were weighed before use and afterward to determine the volume of blood lost. Pre- and post-treatment blood losses were measured separately. Vital signs (heart rate, carotid and saphenous MAP, and oxygen saturation) were recorded before injury, at the time of injury, every minute for 30 min postinjury, and then every 5 min until an end point was reached. Wound site tem-

perature was recorded for the first 10 min. Repeat assays of fibrinogen, activated clotting time, and complete blood count were obtained at 30 and 60 min postinjury.

Statistical Analysis

The primary outcome measures were blood loss standardized to body weight and survival. For the former, descriptive statistics were computed and then compared using analysis of variance with post hoc pairwise tests. Overall survival rates were evaluated using Pearson's χ^2 test. Survival curves were generated using a commercial software package (STATA, Stata Corp, College Station, Texas) and the equality of the survivor functions was tested using log-rank tests.

RESULTS

All 30 animals (6 per group) completed the study with no exclusions. No significant differences existed between groups for any preinjury physiologic or hematologic parameter measured (see Table II). Pretreatment blood loss averaged 7.1 mL/kg with no significant differences between the groups. Postinjury characteristics are described in Table III. There were no significant differences in core temperature, blood counts, fibrinogen, or activated clotting time at 30 min postinjury between the treatment groups.

Overall survival to 120 min and actual survival time were significantly better for all hemostatic agents compared to the

TABLE II. Pretreatment Animal Characteristics

	AFD	ACS+	HC	CX	WS	ANOVA <i>p</i> value
Weight (kg)	43.2 ± 1.4	42.3 ± 1.1	43.7 ± 0.8	43.2 ± 1.7	43.5 ± 1.7	0.967
Preinjury MAP (mmHg)	65.0 ± 3.6	70.5 ± 4.5	63.2 ± 4.6	69.2 ± 3.9	60.5 ± 6.0	0.444
Preinjury Temperature (°C)	36.6 ± 0.2	36.9 ± 0.2	36.6 ± 0.2	36.2 ± 0.3	36.9 ± 0.3	0.255
Preinjury ACT (seconds)	66.7 ± 3.6	70.5 ± 4.6	73.0 ± 6.2	77.7 ± 3.7	69.2 ± 5.6	0.574
Preinjury WBC (×10 ³ /μL)	15.8 ± 0.5	17.0 ± 2.7	15.5 ± 0.5	14.8 ± 0.8	17.7 ± 2.2	0.705
Preinjury Hematocrit (%)	26.2 ± 1.4	26.2 ± 1.3	25.5 ± 1.2	26 ± 0.8	25.9 ± 0.8	0.990
Preinjury Platelets (×10 ³ /μL)	272 ± 33	244 ± 16	239 ± 20	253 ± 19	262 ± 29	0.868
Preinjury Fibrinogen (mg/dL)	267 ± 72	270 ± 67	280 ± 53	233 ± 56	400 ± 52	0.280
Pretreatment Blood Loss (mL/kg)	8.3 ± 0.8	6.4 ± 0.9	7.3 ± 1.2	7.6 ± 0.8	6.0 ± 1.3	0.522

AFD, army field dressing; ACS+, QuikClot advanced clotting sponge +; HC, enhanced HemCon dressing; CX, Celox granules; WS, WoundStat granules; ACT, activated clotting time; WBC, white blood cell count.

TABLE III. Post-Treatment Animal Characteristics

	AFD	ACS+	HC	CX	WS	ANOVA <i>p</i> value
Temperature (°C) at 10 min	36.5 ± 0.3	36.8 ± 0.1	36.6 ± 0.2	36.2 ± 0.3	36.8 ± 0.3	0.406
MAP (mmHg) at 30 min	22.0	54.0 ± 9.0	52.3 ± 0.8	49.0 ± 3.1	50.8 ± 4.3	0.195
ACT (seconds) at 30 min	57.0	52.0 ± 1.4	54.8 ± 2.5	63.6 ± 6.8	55.2 ± 2.4	0.560
WBC (×10 ³ /μL) at 30 min	5.9	21.7 ± 3.4	14.1 ± 0.7	16.4 ± 1.4	17.7 ± 2.6	0.153
Hematocrit (%) at 30 min	20.7	22.5 ± 1.4	23.8 ± 0.8	23.5 ± 0.8	23.7 ± 1.2	0.804
Platelets (×10 ³ /μL) at 30 min	196	233 ± 24	160 ± 40	228 ± 14	220 ± 14	0.393
Fibrinogen (mg/dL) at 30 min	200	200 ± 41	375 ± 147	440 ± 149	216 ± 70	0.637
Survival Time (min)	21.5 ± 6.4	64.5 ± 24.8	83.2 ± 23.3	110 ± 10	120 ± 0	0.002
Survival to 120 min	0/6	3/6	4/6	5/6	6/6	0.005
Post-Treatment Blood Loss (mL/kg)	27.0 ± 2.7	15.8 ± 3.6	10.0 ± 3.6	12.9 ± 4.9	4.6 ± 2.3	0.002

AFD, army field dressing; ACS+, QuikClot advanced clotting sponge; HC, enhanced HemCon dressing; CX, Celox granules; WS, WoundStat granules; ACT, activated clotting time; WBC, white blood cell count. Data included only for animals surviving to given time point. Single surviving animal in AFD group at 30 min precludes confidence intervals.

AFD; a survival curve is shown in Figure 1. WS was the only agent to achieve 100% survival followed by CX (83%), HC (67%), then ACS+ (50%). Five of six AFD animals died by 18 min with a single pig surviving 53 min. In pairwise comparisons survival time for the WS group was significantly better than for ACS+ ($p = 0.05$), but there were no other significant differences between the other dressings.

Post-treatment blood loss was significantly improved for all hemostatic agents when compared with the AFD. As shown in Table III, WS had the lowest blood loss followed by HC, CX, and then ACS+. The WS group had significantly less blood loss than ACS+ ($p = 0.02$), and there were no significant differences in blood loss between the other groups.

A graph of mean arterial pressure (MAP) over time for all groups is shown in Figure 2. The control group rebled shortly after release of pressure with resultant drop in MAP. Other than one late rebleed and death in the CX group from 40 to

60 min, the MAP curves for the hemostatic agents approximate each other closely from 25 min until the end of observation.

Application site temperatures for AFD, CX, HC, and WS were all below 99°F. Peak temperatures in ACS+ applications occurred between 2 and 4 min. The highest recorded temperature for ACS+ of 105.9°F occurred at 4 min and decreased to 103.8°F by 10 min. This heat could be felt through the overlying AFD but was not uncomfortable.

Although blood flow distal to the site of injury and hemostatic agent was not directly measured in this study, an arterial catheter in the ipsilateral thigh demonstrated diminished but measurable arterial pressures in all groups (data not shown).

DISCUSSION

This study demonstrates the superiority of newer hemostatic agents compared to the standard field dressing. While tourniquets are being applied in military field conditions for the majority of exsanguinating extremity trauma, hemostatic agents may play a significant role treating anatomic sites that are not amenable to tourniquet usage such as the groin or axilla. The model of swine groin injury we used is based upon similar studies^{18,19,23} with some modifications. We simulated a complex groin injury with a reproducible near-transection of the femoral artery and vein, causing life-threatening hemorrhage that would be difficult or impossible to treat with a tourniquet. The purpose of the near-transection injury is to prevent vessel retraction, which has contributed to premature hemostasis in studies employing a complete femoral transection model.^{16,17,20-22} While all animal models are necessarily artificial, our modifications were intended to more closely approximate real-world conditions. Specifically, we did not administer lidocaine, thus allowing vasospasm to occur as would be expected in a traumatic injury. This resulted in less pretreatment blood loss than noted in other studies (7.1 mL/kg compared with approximately 16–18 mL/kg).^{18,19}

Furthermore, rather than giving large volumes of saline to achieve a particular MAP (over 120 mL/kg administered in some studies),^{18,19} we limited fluids to 500 mL of hetastarch solution beginning 15 min after injury, which is more consistent with a field resuscitation scenario. This resulted in a MAP of approximately 55 mmHg at 60 min in surviving animals, whereas the above-noted studies resuscitated to a goal MAP of 65 mmHg. However, our results demonstrate that this model provided a rigorous challenge for the hemostatic agents, as evidenced by the separation between the various dressings in terms of overall survival and blood loss. This may be due to our addition of a venotomy where previous incomplete transection studies used an arteriotomy only.^{18,19,23}

The handling characteristics of these agents differ remarkably. The improved handling of the ACS+ allowed it to be removed completely and far more easily than the other agents. Additionally, the heat generated was much less than the original QuikClot granules. The enhanced HemCon bandage was thinner and more pliable and formed a tight seal to the injury that is difficult to remove. In several cases it tore

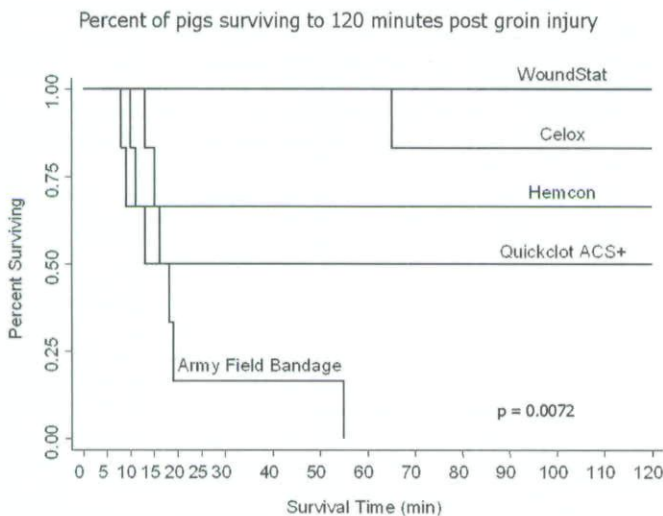


FIGURE 1. Percentage of pigs surviving to 120 min post groin injury.

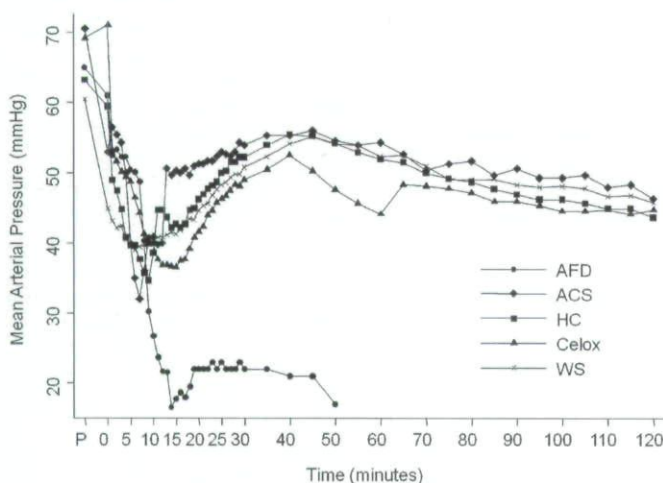


FIGURE 2. Mean arterial pressure in pigs receiving either army field dressing (AFD), HemCon (HC), QuikClot advanced clotting sponge+ (ACS), Celox (CX), or WoundStat (WS).

during removal, but we were always able to completely remove the dressing. Celox produced a sticky granular gelatinous substance that was difficult to remove completely given the wide spread of the granules throughout the wound. WoundStat swelled slightly and developed a red clay-like texture that was easily molded to the wound. It was more difficult to remove than Celox, and both of these substances would require copious irrigation for complete removal. Overall, none of these dressings should be considered definitive care, and all would require removal for operative exploration and repair.

Based on blood loss and survival data, all tested agents are superior to a standard gauze dressing. In addition, WoundStat was superior to the QuikClot ACS+ dressing with a trend toward superiority when compared to the other dressings; however, this study was not sufficiently powered to determine this statistically.

We made no evaluation of the toxicity of these dressings. A recent study at the Army Institute of Surgical Research has shown a moderate inflammatory reaction associated with Celox and tissue damage associated with WoundStat, while ACS+ and HemCon cause minimal histologic changes.²⁵ Furthermore, despite some differences in the model utilized, their findings with regard to efficacy are consistent with, and reinforce, the trends and findings in our study. Further work is needed to determine the long-term effects, if any, of retained agent and whether granular embolization may cause adverse events.

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